Egyptian Journal of Neurosurgery

REVIEW

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Efficacy of hypertonic saline and mannitol in patients with traumatic brain injury and cerebral edema: a systematic review and meta-analysis

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Abstract

Background Traumatic brain injury has a crippling impact on sufferers' quality of life, and numerous therapy techniques are being researched to address this problem. In this study, we compared the superiority of HS against mannitol as one such element of treating TBI patients.

Objective To compare the efficacy of hypertonic saline and mannitol and demonstrate superiority of one group over the other.

Method Our meta-analysis included only randomized controlled trials that compared the efficacy of mannitol and hypertonic saline in the treatment of traumatic brain injury. The literature search was done using a variety of databases, like Google Scholar, PubMed, and the Cochrane Library. From each of the included RCTs, accurate data extraction, bias risk assessment, and statistical analysis were carried out.

Result There are 748 patients among the 15 RCTs. Our primary outcomes are mortality and functional outcomes, and our secondary outcomes include treatment failure, osmolality, intracerebral pressure (ICP), cerebral perfusion pressure (CPP), serum sodium (Na), partial pressure of oxygen in brain tissue (PBTO2), duration of elevated ICP, mean arterial pressure, hematocrit level, and central venous pressure. The comparison showed non-significant results for mortality (RR = 0.73, 95% CI 0.49–1.08; p = 0.12) and functional outcome (RR = 1.15, 95% CI = 0.74–1.80; p = 0.53). HS is linked to higher Na levels (RR = 4.55, 95% CI 1.34–7.76, P = 0.005, I2 = 96%). Despite performing a sensitivity analysis due to the heterogeneities in our various outcomes, the findings were still unreliable.

Conclusion Our study revealed inconsequential trends for HS and mannitol, and no conclusion was made. We believe the two medications to be equally effective, but there is still opportunity for improvement as more studies are carried out. Eventually, a conclusive decision can be reached in the future.

Keywords Saline, Mannitol, Osmotic diuretic, Brain injury, TBI, Craniotomy, Brain edema

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Introduction

Any disruption in the normal anatomic or physiologic functioning of the brain inflicted mainly by external deforming force is defined as traumatic brain injury [1]. TBI has evolved to be a significant contributor to local as well as global causes of mortality [2]. Traumatic brain injury (TBI) can result in both primary and secondary injury processes in the brain [3]. TBI is estimated to be a cause of morbidity in as many as 50 million people with lower-income and middle-income countries being the most affected [1]. One of the most typical signs of traumatic brain damage is intracranial pressure (ICP) monitoring. There are various methods and guidelines proposed for ICP measurement one of which is the Brain Trauma Foundation guidelines. According to Brain Trauma Foundation (BTF) guidelines, which are supported by a study in the TBI database in Cambridge, UK, there is broad agreement in Europe that ICP values above 20 mmHg should be carefully maintained [4]. First-line treatments which are found significant such as hypocapnia, hyperosmolar medications, and general practices such as normothermia, and sedation are initiated at the same time. In the longer run decompressive craniectomy is carried out, when none of these techniques are found fruitful [5]. Osmotic drugs are potentially advantageous in reducing high intracranial pressure, increasing cerebral perfusion pressure, and significantly increasing cerebral blood flow [6]; therefore, after a debilitating brain injury (TBI), mannitol and hypertonic saline (HTS) are both used to lower intracranial pressure (ICP) [7, 8]. According to the Traumatic Brain Injury Foundations, there are inadequate data from published studies and no affirmation to support the use of any specific hyperosmolar drug in patients with severe traumatic brain injury (TBI) for the treatment of severe traumatic brain injury (TBI) [9] However, some research suggests that HS is superficial to mannitol in terms of reducing oxidative stress, fewer adverse effects, and maintaining CPP [10–12]. Animal studies suggest that hypertonic saline is beneficial in reducing pro-inflammatory markers. However, human studies have not confirmed these results [13]. There are numerous problems encountered in already published meta-analyses, ranging from ineffective search strategies to methodological errors which can be so minute that can be ignored or may cause a significant bias in the overall outcomes [14]. Among various other confounding factors include failure to collect appropriate data, usage of erroneous methods, and not following the specified selection criteria. Detailed study of the literature has shown that insufficient information is available to choose one option over another and thus requires extended research in this area [15, 16]. Therefore, it is still not clear whether HS is better than mannitol for treating people who have suffered traumatic brain injury. Our meta-analysis aimed to determine how HS compares to mannitol in terms of mortality, functional outcome, and cerebral physiological factors in TBI patients.

Methods

Eligibility criteria

The meta-analysis includes only randomized controlled trials (RCTs) investigating the effect of hyperosmolar therapy (hypertonic saline or mannitol) on patients with traumatic brain injury (TBI) or cerebral edema secondary to brain injury. Studies with TBI patients in the subgroup were also eligible for meta-analysis. Studies with all drug doses of hypertonic saline and mannitol were included. All patient age groups are reviewed in the study. Other studies, such as observational studies, reviews, case reports, and the use of solutions other than hypertonic saline and mannitol, were excluded. Reasons for exclusion of studies not meeting our inclusion criteria are given in Additional file 1 (Table S01).

Search strategy

The search was done with the use of terms like "saline, mannitol, osmotic diuretic, brain injury, craniotomy, brain edema" in electronic databases PubMed, Cochrane Library, and Google Scholar. In addition to searching the database, a manual search was also conducted. The selection of randomized control studies was made with no language-based exclusions. This thorough search technique was created to provide us with relevant clinical trials comparing mannitol and hypertonic saline for the treatment of TBI. Search strategy table is given in Additional file 1 (Table S2).

Study selection

The titles and abstracts of the collected data were examined as part of the research selection process to find studies that might be relevant. The full texts of the chosen publications were then analyzed, and two researchers reviewed them for selection in the meta-analysis. Any conflicts were solved by discussion with the third researcher. To improve transparency in the review process, the PRISMA flowchart (Fig. 1) was used to demonstrate the research selection process and the justifications for omitting studies.

Data extraction and risk of bias assessment

Data extraction

We extracted baselines, intervention specifics, patient counts, dichotomous data, and continuous data from each of the selected RCTs and supplemental RCTs. Our study's primary outcomes were mortality and favorable

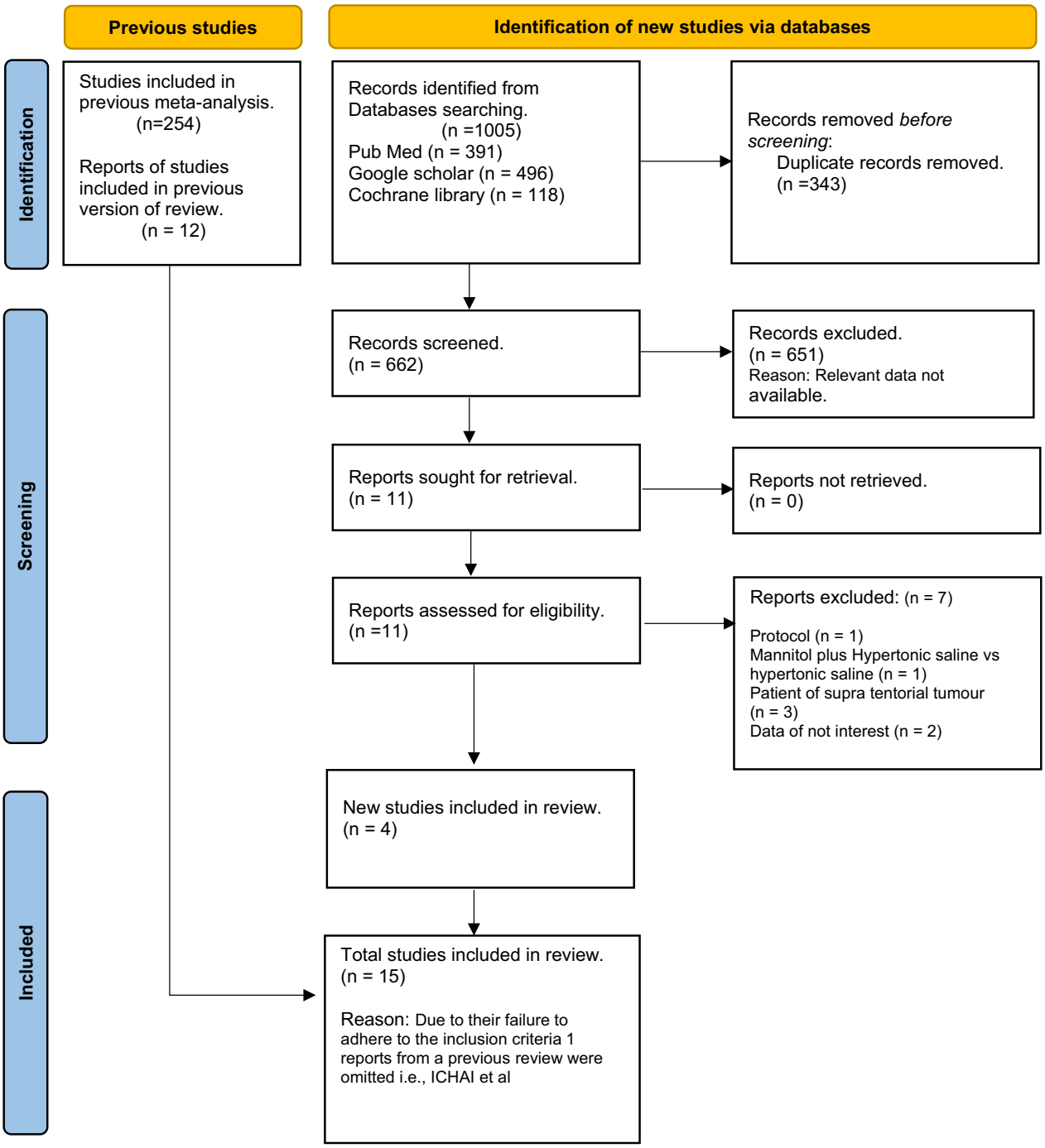

Fig. 1 PRISMA flow diagram

outcomes. Both sets of data were dichotomous. The Glasgow Outcome Scale (GOS) or the extended Glasgow Outcome Scale (GOSE) was used to evaluate the outcome, and a GOS or GOSE score of ≥ 4 or ≥ 5, respectively, was considered a favorable outcome. Secondary outcomes included hematocrit level, treatment failure, serum sodium (Na+), intracerebral pressure (ICP), cerebral perfusion pressure (CPP), brain tissue partial pressure of oxygen (PBTO2), osmolality, duration of elevated ICP, mean arterial pressure (MAP), and central venous pressure (CVP).

Risk of bias assessment

Two selected authors used the Cochrane Collaborations tool for assessing the probability of bias in randomized studies to formally evaluate the quality of the chosen studies. The assessment of bias was based on the use of outcome blinding, the availability of outcome data, the fact that the study's results were reported solely in some cases, and other additional sources of bias. Low risk of bias, high risk of bias, and unclear risk of bias (lack of information) are the three categories into which the studies were classified. Risk of Bias Assessment by Cochrane Risk of Bias Tool is given in Additional file 1 (Table S03). The studies classified as "high risk" > 1 underwent a sensitivity analysis as well (Fig. 2) and Additional file 1 (Figure S1). A visual interpretation using a funnel plot was used to account for the possibility of publication bias.

Statistical analysis

In this meta-analysis, we used RevMan 5.2 (Review Manager v.5.2) to analyze all data. A random effects model was used in all statistics in the study. Dichotomous data were represented by relative risk (RR) or risk difference with a 95% confidence interval (CI), and continuous data by mean difference (MD) with a 95% CI. The p value of < 0.05 is considered a statistically significant result, and statistical heterogeneity was analyzed visually using the forest plot by χ^2 test and I2 test. A P value < 0.5 or I2 > 50% was considered high heterogeneity, and when high heterogeneity was found, we performed a leave-one-out analysis to rule out the cause.

Results

Study characteristics

In our literature screening, we found 1005 total studies by using our search string; however, after matching our inclusion criteria, only 15 studies [5, 17–29] were found eligible and used for our meta-analysis, all of them being RCTs. The PRISMA flowchart is a brief review of our screening. Our sample size included males as well as females, and the sample size range included the pediatric population as well as the adult population. The total number of participants was 748. Our study intervention included different percentages of hypertonic saline: 7 RCTS used 3% HS [1, 2, 2, 3, 3–7, 7–15], 5 studies used 7.5% HS [4, 5, 8–10], and 10%, 5%, and 15% HS was used by the rest of the three RCTs [1, 6, 11], respectively. However, the control group was the same in all studies, i.e., 20% mannitol. Information about the baseline characteristics of all studies is given in Table 1.

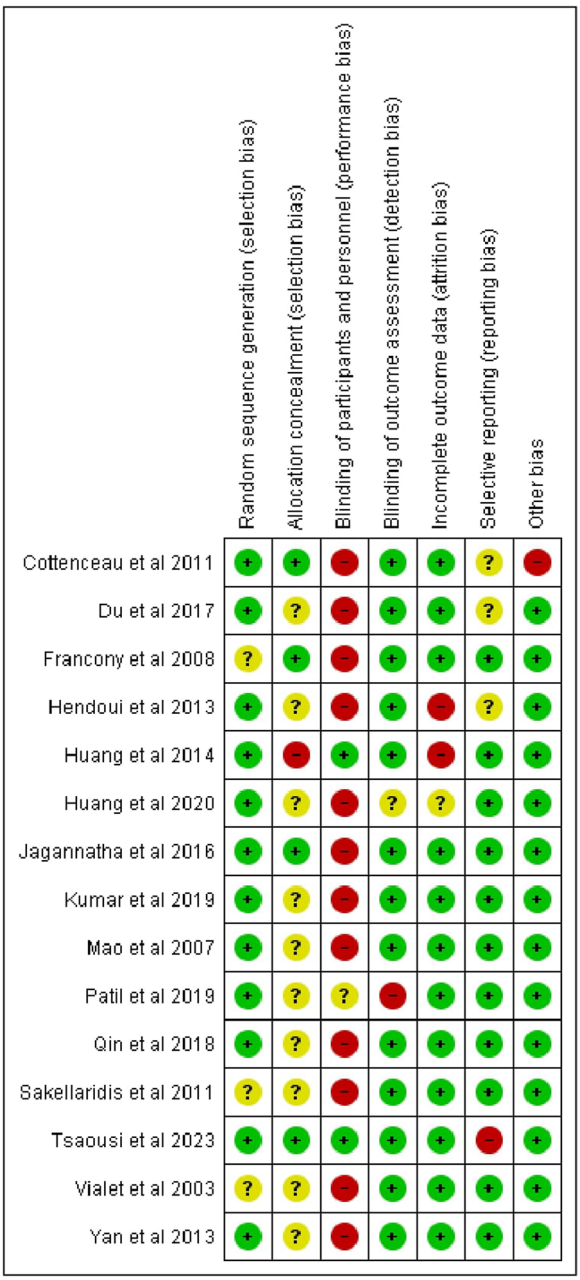

Fig. 2 Risk of bias summary showing the authors' judgments about each risk of bias item for each included study

Primary outcomes

The primary outcomes of our study, as defined by PICO criteria, were mortality and functional outcomes. Our main aim in performing this meta-analysis was to find out whether HS or mannitol is superior in reducing brain edema and subsequent mortality and functional outcomes. During our study assessment, 7 out of 15 RCTs reported mortality at the end of follow-up [3, 5–8, 12, 13]. Our analysis showed a non-significant trend

Table 1 Baseline characteristics of included studies

Author	Year	Country	Design	Intervention fluid	Control fluid	Patients	Outcomes
Huang et al. [17]	2020	China	RCT	10% HS	20% M	Severe TBI with ICH	Repeated doses of 10% HTS and 20% M seems equally effective in treating ICH. HTS might have a slightly better role in changing ICP and CCP compared to M
Patil and Gupta [18]	2019	India	RCT	3% HS	20% M Plus 10% M and 10% Glycerol	Severe TBI, GCS ≤ 8, ICP > 20 mmHg, > 5 min	Maximum changes in ICP, CCP and GCS occurred with 3% HTS followed by 10% M Plus 10% glycerol combo then 20% M. Better neurological outcome ē HTS and M + Glyc. Combo
Kumar et al. [19]	2019	India	RCT	3%HS	20% M	Children with severe TBI and raised ICP	Both mannitol and hypertonic saline were equally effective for treatment of raised ICP
Tsaousi et al. [20]	2023	Greece	RCT	7.5% HS	20% M	undergoing elective supratentorial craniotomy	HTS and M showed no significant differences. However, HTS had improvements in cerebral oxygenation and reduced neuronal damage compared to mannitol
Du et al. [30]	2017	China	RCT	3% HS	20% M	Severe TBI ICP > 20 mmHg	HS was better than M in reducing ICP. Clinical outcome was not significantly improved
Cottenceau et al. [21]	2011	France	RCT	7.5% HS	20% M	Severe TBI ICP > 15 mmHg	HS and M both reduced ICP and increased CPP
Hendoui et al. [22]	2013	Iran	RCT	5% HS	20% M	Moderate to severe TBI. Scheduled therapy	S100B useful for treatment monitoring HS safe and effective in TBI
Jagannatha et al. [23]	2016	India	RCT	3% HS	20% M	Severe TBI ICP > 20 mmHg > 10 min	HS: shorter duration of increased ICP and inotrope requirement
Qin et al. [31]	2018	China	RCT	3% HS	20% M	Severe TBI, after decompressive Craniectomy ICP > 20 mmHg > 5 min	HS can decrease postoperative complications, and improve the prognosis of patients
Vialet et al. [24]	2003	France	RCT	7.5% HS	20% M	Severe TBI ICP > 25 mmHg > 5 min	Less ICP episodes and treatment failure in HS group
Francony et al. [25]	2008	France	RCT	7.5%HS	20% M	TBI and stroke ICP > 20 mmHg > 10 min	HS and M both reduced ICP effectively
Huang et al. [26]	2014	China	RCT	7.5% HS	20% M	Severe TBI ICP > 20 mmHg > 5 min	HS and M similar on maximum ICP reduction, action onset, and duration of action
Mao et al. [32]	2007	China	RCT	3% HS	20% M	Severe TBI, after decompressive Craniectomy ICP > 20 mmHg > 5 min	HS and M rapidly decrease ICP; HS has a longer duration of action
Sakellardis et al. [27]	2011	Greece	RCT	15% HS	20% M	Severe TBI ICP > 20 mmHg > 5 min	HS and M equal on ICP reduction and duration of action
Yan et al. [33]	2013	China	RCT	3% HS	20% M	Severe TBI after decompressive Craniectomy ICP > 25 mmHg > 5 min	HS can rapidly decrease ICP and increase MAP without obvious side effects

toward low mortality in the group that was administered HS as compared to the control group that used mannitol. The combined risk ratio of 15 studies was 0.73 (95% CI 0.49, 1.08: p = 0.12, I2 = 0%). These results show that there are no significant trends toward the use of HS with lower mortality as compared to mannitol. There was also no significant heterogeneity in mortality outcome. A forest plot of mortality outcome is given in Fig. 3.

During the analysis of our second primary outcome, i.e., functional outcomes, we found four studies [5, 7, 12, 13] reporting positive results for functional outcomes. The combined risk ratio for these 4 studies showed a non-significant trend toward mannitol, which was our control group, at 1.15 (95% CI 0.74, 1.80: p = 0.53, I2 = 41%). A

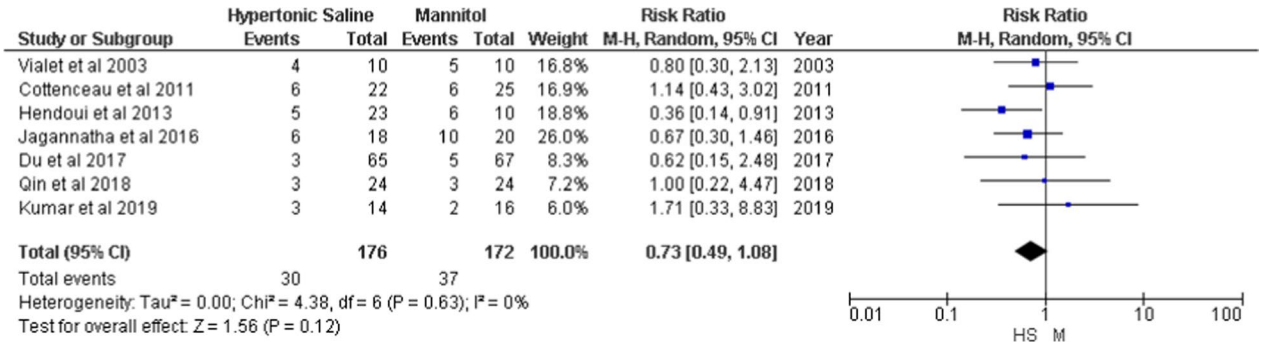

Fig. 3 Forest plot of mortality at end-of-study follow-up

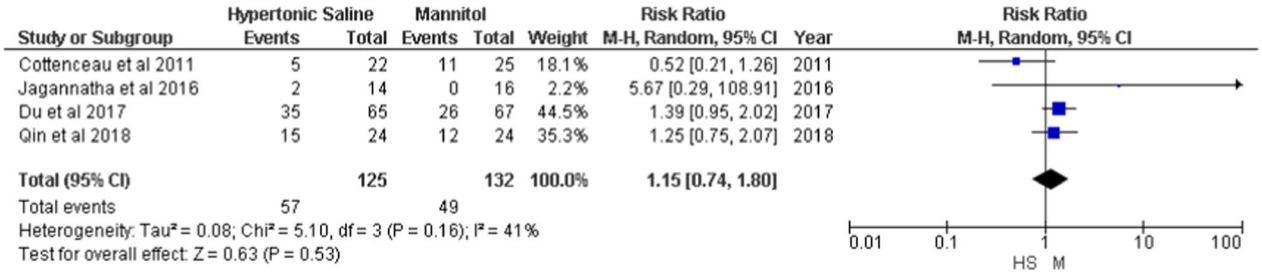

Fig. 4 Forest plot of favorable outcome at end-of-study follow-up

forest plot of mortality outcome is given in Fig. 4. In the analysis of functional outcomes, moderate heterogeneity was found. Here, we performed a sensitivity analysis to assess the risk of bias by using the leave-one-out method, but the results remained inconclusive. However, it is noteworthy to mention that the small number of studies can derange the precision of the studies and result in invaluable results.

Secondary outcomes

Various secondary outcomes were found in the range of RCTs we used for our meta-analysis. Some of them were significant enough, while others were not that significant. The forest plot of all the secondary outcomes is attached in the supplementary file. A brief review of all the secondary outcomes encountered is given below.

Intracranial pressure monitoring (30–60 min)

Twelve studies were included in the analysis, which measured ICP at 30–60 min intervals [1–3, 5, 7, 9–15]. Pooled analysis of the twelve studies shows that the risk ratio using the random effect model was found to be 0.04 (95% CI −0.51, 0.58: p = 0.90, I2 = 47%). The statistical analysis shows that there is no significant difference between usage of HS and mannitol at 30–60 min intervals; however, the analysis shows moderate heterogeneity for which sensitivity analysis was performed using leave one out, and yet there was no significant change in heterogeneity. Figure of forest plot and funnel plot of ICP at 30–60 min is given in Additional file 1 (Figures S2 and S16).

Intracranial pressure monitoring (90–120 min)

Five studies were included in the analysis [1, 2, 5, 9, 13] which measured ICP at 90–120 min intervals. Pooled analysis of the five studies shows that the risk ratio using the random effect model was found to be 0.58 (95% CI −2.57, 1.43 p = 0.57, I2 = 81%). The statistical analysis shows that there is no significant difference between usage of HS and mannitol at 90–120 min intervals; however, the analysis shows a high heterogeneity for which sensitivity analysis was performed using leave one out, and yet there was no significant change in heterogeneity. Figure of forest plot is given in Additional file 1 (Figure S3).

Cerebral perfusion pressure monitoring (30–60 min)

Six studies were included in the analysis [1–3, 5, 9, 10] which measured CPP at 30–60 min intervals. Pooled analysis of the six studies shows that the risk ratio using the random effect model was found to be 33.20 (95% CI −72.29, 5.89: P = 0.10, I2 = 100%). The statistical analysis shows that there is no significant difference between usage of HS and mannitol at 30–60 min intervals; however, the analysis shows a high heterogeneity for which sensitivity analysis was performed using leave one out,

and yet there was no significant change in heterogeneity. Figure of forest plot is given in Additional file 1 (Figure S4).

Cerebral perfusion pressure monitoring (90–120 min)

Four studies were included in the analysis [1, 2, 5, 9] which measured CPP at 90–120 min intervals. Pooled analysis of the four studies shows that the risk ratio using the random effect model was found to be 3.73 (95% CI −0.51, 7.97: P = 0.08, I2 = 73%). The statistical analysis shows that there is no significant difference between usage of HS and mannitol at 90–120 min intervals; however, the analysis shows high heterogeneity, for which sensitivity analysis was performed using leave one out, and a change in heterogeneity was found that was not significant. Figure of forest plot is given in Additional file 1 (Figure S5).

Leave one out of the analysis

The pooled analysis of four RCTs showed a risk ratio of 3.73 (95% CI −0.51, 7.97: P = 0.08, I2 = 73%). Since the heterogeneity was high, a leave-one-out analysis was performed, which dropped from high to moderate, but the results were still insignificant. Patil et al. 2019 [18] was ruled out as the cause of high heterogeneity. However, a small sample size and a smaller number of studies can cause a disturbance in the accuracy of results. Figure of forest plot is given in Additional file 1 (Supplementary Fig. 6).

Brain tissue oxygenation monitoring (PBTO2) at 30–60 min

Only one study [25] was included in the analysis, which measured PBTO2 at 30–60 min intervals. Analysis of the study shows that the risk ratio using the random effect model was found to be −1.41 (95% CI 5.16, 2.34: P = 0.46, I2 = not applicable). The statistical analysis shows that there is no significant difference between the usage of HS and mannitol at 30-60 min intervals. Also, heterogeneity was ruled out for this parameter because of the limitation to one RCT only. Figure of forest plot is given in Additional file 1 (Figure S7).

Brain tissue oxygenation monitoring (PBTO2) at 90–120 min

Only one study [25] was included in the analysis, which measured PBTO2 at 90–120 min intervals. Analysis of the study shows that the risk ratio using the random effect model was found to be −1.44 (95% CI 3.88, 1.00: P = 0.25, I2 = not applicable). The statistical analysis shows that there is no significant difference between the usage of HS and mannitol at 90-120 min intervals. Also, heterogeneity was ruled out for this parameter because of the limitation to one RCT only. Figure of forest plot is given in Additional file 1 (Figure S8).

Temperature monitoring

Three studies [23, 24, 32] were included in the analysis that measured treatment failure. Pooled analysis of the three studies shows that the risk ratio using the random effect model was found to be 0.55(95% CI −0.21, 1.46: P = 0.23, I2 = 47%). The statistical analysis shows that there is no significant difference between the usage of HS and mannitol. However, the analysis shows moderate heterogeneity, for which sensitivity analysis was performed using leave one out, and a change in heterogeneity was found that was not significant. Figure of forest plot is given in Additional file 1 (Figure S9).

Duration of elevated ICP [h/d]

Four studies [21, 23, 24, 28] were included in the analysis that measured the duration of elevated ICP [h/d]. Pooled analysis of the four studies shows that the risk ratio using the random effect model was found to be 0.41 (95% CI −4.52, 5.34: P = 0.87, I2 = 97%). The statistical analysis shows that there is no significant difference between the usage of HS and mannitol. However, the analysis shows high heterogeneity, for which sensitivity analysis was performed using leave one out, and a change in heterogeneity was found that was not significant. Figure of forest plot is given in Additional file 1 (Figure S10).

Mean arterial pressure measurement

Seven studies [17–23] were included in the analysis that measured mean arterial pressure. Pooled analysis of the seven studies shows that the risk ratio using the random effect model was found to be 0.20 (95% CI 4.73, 5.14: P = 0.94, I2 = 86%). The statistical analysis shows that there is no significant difference between the usage of HS and mannitol. However, the analysis shows high heterogeneity, for which sensitivity analysis was performed using leave one out, and a change in heterogeneity was found that was not significant. Figure of forest plot is given in Additional file 1 (Figure S11).

Cerebral venous pressure monitoring

Two studies [17, 20] were included in the analysis that measured central venous pressure. Pooled analysis of the two studies shows that the risk ratio using the random effect model was found to be 0.21 (95% CI −0.26, 0.68: P = 0.38, I2 = 0%) The statistical analysis shows that there is no significant heterogeneity difference between the usage of HS and mannitol. Figure of forest plot is given in Additional file 1 (Figure S12).

Measurement of osmolality

Six studies [17, 18, 20, 22, 23, 25] were included in the analysis that measured serum osmolality levels. Pooled analysis of the 6 studies shows that the risk ratio using the

random effect model was found to be 3.07 (95% CI −2.28, 8.41: P = 0.26, I2 = 82%) The statistical analysis shows that there is no significant difference between the usage of HS and mannitol in serum osmolality. However, the analysis shows a high heterogeneity, for which sensitivity analysis was performed using leave one out, and a change in heterogeneity was found that was not significant. Figure of forest plot is given in Additional file 1 (Figure S13).

Leave one out of the analysis

The pooled analysis of 6 RCTs showed a risk ratio of 1.14 (95% CI −0.79, 3.06: P = 0.25, I2 = 0%). Since the heterogeneity was high, a leave-one-out analysis was performed, which dropped the heterogeneity level from high to negligible, but the results were still insignificant. Patil et al. 2019 [18] was ruled out as the cause of high heterogeneity. However, a small sample size and a smaller number of studies can cause a disturbance in the accuracy of results. Figure of forest plot is given in Additional file 1 (Figure S14).

Measurement of hematocrit levels

Two studies [18, 21] were included in the analysis that measured hematocrit levels. Pooled analysis of the 2 studies shows that the risk ratio using the random effect model was found to be −1.79 (95% CI −4.29, 0.72: P = 0.16, I2 = 56%). The statistical analysis shows that there is no significant heterogeneity difference between the usage of HS and mannitol. However, sensitivity analysis was performed for moderate heterogeneity, but the results were inconclusive. Figure of forest plot is given in Additional file 1 (Figure S15).

Measurement of sodium levels

Eight studies [17–23, 25] were included in the analysis that measured sodium levels. Pooled analysis of the 8 studies shows that the risk ratio using the random effect model was found to be 4.55 (95% CI 1.34, 7.76: P = 0.005, I2 = 96%). The statistical analysis shows that there is a significant heterogeneity difference between the usage of HS and mannitol. A sensitivity analysis was performed for high heterogeneity, but the results were inconclusive. Figure of forest plot is given in Additional file 1 (Figure S16).

Discussion

We performed an updated meta-analysis on the effect of hypertonic saline and mannitol on traumatic brain injury [34]. The reason for updating our previous meta-analysis is that newer studies were published that would change the outcome of the previously published meta-analysis. Our summary of the results showed the difference between the two groups in both the primary endpoints and the secondary endpoints. Our primary endpoints included differences in mortality and functional outcomes. Our secondary endpoints included differences between both groups in ICP at 30–60 min, ICP at 90–120 min and CPP at 30–60 min, CPP at 90–120 min, brain tissue oxygen monitoring (PBTO2) at 30–60 min, (PBTO2) at 90–120 min, temperature monitoring, duration of elevated ICP [h/d], measurement of mean arterial pressure, monitoring of cerebral venous pressure. The results of the primary and most of our secondary endpoints were not significant. However, some studies favor HS over mannitol in some of the outcomes we use such as ICP monitoring, as well as serum osmolality and sodium elevation, and some suggest that mannitol is equally effective in reducing ICP [25], but comorbidities should be assessed before starting treatment [35]. In the analysis, we measured the required sample as with RCTS, but our sample size was a bit small. The correlation between different outcomes and GCS is limited in severe traumatic brain injury [36].

The Schwimmbeck [34] study showed that HS was superior to mannitol for mortality and functional outcome, and our study found similar results for mortality, but for functional outcome, our study preferred mannitol; however, our results were not significant but we found moderate heterogeneity in our outcome for which leave-one-out analysis was performed with inconclusive results. Our sample size was slightly larger, which may have been a cause of our results being non-significant. In our secondary outcomes, we included treatment failure, CVP, osmolality, hematocrit, and Na^+ score maps as our results, which original meta-analysis did not consider. Schwimmbeck [34] showed no significant differences in ICP between both groups in the first hour but favored HS over mannitol in ICP reduction in the second hour. Meanwhile, our study found that HS slightly increases ICP in the first hour, but then decreasing it in the second hour; however, overall results were not significant. For CPP, Schwimmbeck [34] showed that HS is beneficial at both 1st and 2nd hour, but our studies showed a better CPP response in the Mannitol group at the 1st hour, followed by a better response in the HS group in the second hour, but our results were not significant. There was only one study by [25] showing the effect on PBTO2, but the results were not significant. All other results were non-significant, except for the sodium values, which showed a significant trend toward mannitol. Although we included some new results, only one of them, the effect of both groups on sodium (Na) levels, was significant and favored our control group, i.e., mannitol.

Although there are differences in the ICP between the two groups, i.e., HS and mannitol, and differences in the CPP, the results are not significant. Apart from that, HS has a larger hemodynamic profile and mannitol is

associated with greater hemodynamic instability [34]; however, we could not provide any valid reason to support this finding. Some non-randomized studies also suggest that HS is beneficial in cases where ICP is resistant to mannitol [37, 38]. Despite the utility of PBTO2 monitoring in TBI [39], we could only include one study showing the effect of PBTO2 monitoring [2]. There were also only two studies looking at hematocrit levels [18, 21], despite their role in the need for TBI management [40]. Rare side effects are unlikely to be observed in RCTs with small sample sizes; however, in this analysis, we have discussed side effects in various RCTs. An RCT showed that HS is associated with an increased risk of bloodstream infections in patients with severe TBI [41]. Similar observational studies suggest that H(18)S is associated with an increased risk of infection [42, 43], but some studies also suggest a lower risk of infection [44]. Our study showed no complications caused by hypernatremia; however, a retrospective study showed that continuous HS infusion in children was associated with acute renal failure, acute respiratory distress syndrome, thrombocytopenia, and neutropenia [45]. With mannitol, acute renal failure [46, 47] exacerbates cerebral edema [48], hyperkalemia [49, 50], hyponatremia [50]. Mannitol is still a standard drug in intensive care units [51], and hypertonic saline is used in refractory cases [24].

Although we conducted our study with quality standards and reasonable design, there were five limitations. First, our study shows heterogeneity in the different outcomes for which we performed a sensitivity analysis where we performed leave-one-out analysis, but our results remained non-significant. There were 7 of our outcomes that showed high heterogeneity, including ICP (90–120 min), CPP (30–60 min), CPP (90–120 min), duration of elevated ICP, MAP, osmolality, and sodium levels. Sensitivity analysis was performed in all of these scenarios, but no study had an impact, except for CPP (90–120) in which one study [18] changed the heterogeneity from high to moderate. Petit et al. in a 2019 study [18] was excluded as a cause of high heterogeneity and osmolality, which when excluded reduced heterogeneity from high to negligible. But even after that, the results were still not significant. Four of our results showed moderate heterogeneity, namely functional results, ICP (30–60 min), temperature monitoring, and hematocrit values, for which we performed sensitivity analysis, but the change proved to be non-significant, and the heterogeneity of PBTO2 could not be tested since only one RCT was available. Second, our results are not significant; only one result is significant, favoring mannitol, showing that mannitol is associated with decreased sodium levels. Third, for some outcomes, we have a limited number of RCTs, and for others more RCTs, such as 4 RCTs for CPP (90–120 min), 6 RCTs for CPP (30–60 min), and 12 RCTs for ICP (30–60 min). Likewise, we only have 1 RCT for PBTO2 monitoring, 2 for CVP, and 2 for hematocrit. This might have resulted in bias in our findings. Fourth, our population size includes both adults and children, and due to the different body dynamics these two have, we have not been able to demonstrate the effect of HS or mannitol on these individual populations, and we have been unable to see the effect these populations might have had individually influencing our results. Fifth, we used HS and mannitol at all concentrations, so we could not tell if any particular concentration was beneficial or not. We also could not demonstrate which concentrations rendered our results non-significant. Last but not the least, one study that we used in our meta-analysis also included 10% glycerol which was not the part of original plan. These were all limitations we had, but despite these limitations, we tried to find as much conclusive results as possible to advance our knowledge and put forth best of the conclusions.

Conclusions

Overall, we performed the meta-analysis and included a total of 15 RCTs; some of them reported different results, and others reported the same result. We then attempted to analyze the results of the superiority or efficacy of HS, our intervention group, versus mannitol, our control group, for use in emergencies where immediate decisions must be made in the best interests of patients. However, we did not find any notable results, which is due to various reasons that we mentioned in the limitations section. Only one result proved to be significant. Still, more RCTs with controlled settings, larger sample sizes, and proper subgroup analysis will help increase study yield over time. We hope that further studies will be conducted so that we can better understand how patients are treated and treat them in their best interests.

Abbreviations

AK	Aashish Kumar
AR	Adarsh Raja
BTF	Brain Trauma Foundation
CI	Confidence Interval
CNS	Central Nervous System
CPP	Cerebral Perfusion Pressure
CVP	Central Venous Pressure
GCS	Glasgow Coma Scale
GOS	Glasgow Outcome Scale
GOSE	Glasgow Outcome Scale-Extended
HS	Hypertonic Saline
HTS	Hypertonic Saline
ICH	Intracranial Hypertension
ICP	Intracerebral Pressure
JPMC	Jinnah Postgraduate Medical Center
MAP	Mean Arterial Pressure
MAS	Muhammad Ashir Shafique
MD	Mean Difference

PBTO	Continuous Brain Tissue Oxygen
RA	Rabbia Aqeel
RCT	Randomized Controlled Trial
RCTS	Randomized Controlled Trials
RR	Risk Ratio
SAA	Syed Ali Arsal
SBA	Shafin Bin Amin
SW	Sameeka Waqas
TBI	Traumatic Brain Injury
UI	Umer Iqbal
UK	United Kingdom

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41984-023-00233-w.

Additional file 1: Table S01. Reasons for exclusion of studies. **Table S02**: Search strategy table with keywords. **Table S03**: Risk of Bias Assessment by Cochrane Risk of Bias Tool. **Figure S1.** Risk of Bias Graph. **Figure S2.** Forest Plot of ICP (30–60 min). **Figure S3.** Forest Plot of ICP (90–120 min). **Figure S4.** Forest Plot of CPP (30–60 min). **Figure S5.** Forest Plot of CPP (90–120 min). **Figure S6.** Leave-one-out analysis. **Figure S7.** Forest Plot of PBTO**2** (30–60 min). **Figure S8.** Forest Plot of PBTO**2** (90–120 min). **Figure S9.** Forest Plot of Treatment failure. **Figure S10.** Forest Plot of duration of elevated ICP [h/d]. **Figure S11.** Forest Plot of MAP. **Figure S12.** Forest Plot of CVP. **Figure S13.** Forest Plot of Osmolality. **Figure S14.** Leave-one-out analysis. **Figure S15.** Forest Plot of Hematocrit. **Figure S16.** Forest Plot of Na. **Figure S17.** Funnel Plot of ICP (30–60 min)

Acknowledgements
Not applicable.

Author contributions
AK did the study conceptualization and design. AK and SAA conducted the literature search and screening. MAS did the data extraction. Draft manuscript preparation was done by AK, SBA, SAA, and RA. AR performed the analysis and interpretation of results. UI and SW did the compilation and editing. UI did the final editing and supervision. All authors reviewed the results and approved the final version of the manuscript.

Funding
The authors received no extramural funding for this meta-analysis.sak.

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Received: 17 August 2023 Accepted: 10 September 2023
Published online: 02 October 2023

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